UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: September 21, 2004

Subject: **PP3F6754** Human Health Risk Assessment for Proposed Uses of Spinosad on Cereal Grains, (excluding sweet corn)
DP Barcode: D304201
Class: Insecticide
PC Code: 110003

From: William G. Sproat, Jr., PhD
Insecticide Branch/Registration Division (7505C)
J. R. Tomerlin, PhD, ARIA Team Co-Leader
Fungicide Branch/Registration Division (7505C)

Through: P.V. Shah, Ph.D., Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

To: George LaRocca
Insecticide Branch
Registration Division (7505C)

EXECUTIVE SUMMARY

Spinosad is a broad spectrum insecticide which acts by disrupting binding of acetylcholine in nicotinic acetylcholine receptors at the postsynaptic cell. Dow AgroSciences has submitted a petition for the establishment of permanent tolerances for residues of the insecticide spinosad in/on the cereal grains crop group, from the use of spinosad as a seed treatment. Permanent tolerances have been established under 40 CFR §180.495(a) for spinosad *per se*, in or on a wide variety of RACs at levels ranging from 0.02 to 10 ppm. Time-limited tolerances in conjunction with Emergency Exemption registrations have also been established for a wide variety of RACs at levels ranging from 0.02 - 15 ppm, and are listed under 40 CFR §180.495(b). Spinosad is also registered for use on residential turf. However, due to the low vapor pressure of spinosad, no significant homeowner handler inhalation exposure is expected. Therefore, a quantitative homeowner handler inhalation assessment was not performed.

Dow AgroSciences has requested a Section 3 registration for spinosad use on cereal grain seeds. This petition was submitted to establish a Section 3 registration for the 80% wettable powder product Entrust (EPA Reg. No. 62719-282), SpinTor 2SC (EPA Reg. No. 62719-294), and NAF-

313 (EPA Reg. No. 62719-291) as a stored grain protectant applied as a coarse spray to the grain stream.

Spinosad in all formulations would be applied to prevent damage to cereal grain seeds from grain insect pests such as the lesser grain borer, Indian meal moth, Angoumois grain moth, rice weevil, granary weevil, maize weevil, red-flour beetle, saw-toothed grain beetle, and flat grain beetle.

The rates of application vary from 0.64 dry oz. Entrust® (0.032 lb a.i.) per 1,000 bushels to 1.20 dry oz. Entrust® (0.06 lb a.i.) per 1,000 bushels depending upon grain species. SpinTor 2SC rates of application varied from 2.0 fl oz per 1,000 bushels to 3.9 fl oz per 1,000 bushels depending on the type of grain. NAF - 313 rates of application vary from 4.0 fl oz (0.03125 lb a.i.) per 1,000 bushels to 7.8 fl oz (0.061 lb a.i.) per 1,000 bushels depending upon species of grain. One application is permitted. Spinosad will be applied as a coarse spray to the grain "stream" as it is augered or conveyed to a silo or similar storage facility.

The HED Hazard Identification Assessment Review Committee (HIARC) met on July 11, 2002 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to spinosad (see D284803). The FQPA Safety Factor Committee (SFC) met on July 29, 2002 to evaluate the hazard and exposure data for spinosad and recommended that the special FQPA Safety Factor be reduced to 1X in assessing the potential risk posed by this chemical. All hazard-based database factors were also reduced to 1X.

The reference dose (RfD) is equal to the no observable adverse effect level (NOAEL) divided by a 100X uncertainty factor. Risk assessments were conducted for the specific exposure scenarios listed below. The chronic RfD (cRfD) was calculated using the NOAEL and a 100-fold uncertainty factor (10X for interspecies extrapolation and 10X for intraspecies variation), per HIARC. The chronic Population Adjusted Dose (cPAD) is equal to the cRfD divided by the FQPA factor. No endpoint was selected for the acute RfD (aRfD) for all population subgroups due to lack of toxicological effects of concern attributable to a single dose. In estimating margins of exposure (MOEs), the level of concern is for MOEs less than 100 for the inhalation occupational risk assessments. Quantification of dermal risk is not required. Spinosad is classified as "not likely to be carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species. Therefore, a cancer risk assessment is not required. Since oral studies were selected for all durations of inhalation exposure, a 100% inhalation absorption factor is used in the route-to-route extrapolation. No dermal absorption factor was selected because quantification of dermal and cancer risk is not required. The toxicological endpoints relevant to this assessment are summarized below.

Chronic dietary	NOAEL = 2.68 mg/kg/day	chronic RfD and cPAD = 0.027 mg/kg/day
Acute dietary	Oral NOAEL = 2000 mt/kg/day (HDT)	No toxicological effects of concern - acute dietary risk assessment not required
Chronic dietary	Oral NOAEL = 2.68 mg/kg/day	cPAD = 0.027 mg/kg/day
Short-term inhalation	Oral NOAEL = 4.89 mg/kg/day	Target MOE = 100 (occupational)
Short-term incidental oral	Oral NOAEL = 4.89 mg/kg/day	Target MOE = 100 (residential)

Preceding data from Memorandum, P. Shah, 11 July 2002, "SPINOSAD - 2nd Report of the Hazard Identification Assessment Review Committee." PC Code 110003.

The FQPA SFC met on July 29, 2002 and recommended that a traditional additional safety factor of 10X can be removed for spinosad exposures and risks based on the following (Memo, B.Tarplee, HED document # 013341, 07-AUG-2002):

- The toxicological data base for spinosad is complete for FQPA assessment;
- There is no evidence of increased susceptibility of rat or rabbit fetuses following *in utero* exposure in the developmental studies with spinosad, and there is no evidence of increased susceptibility of young rats in the reproduction study with spinosad;
- There are no residual uncertainties identified in the exposure databases;
- EFED has indicated that the dietary drinking water exposure is based on conservative modeling estimates;
- HED Residential SOPs were used to assess post-application exposure to children as well as incidental oral exposure of toddlers, so these assessments do not underestimate the exposure and risks posed by spinosad.

DowAgroSciences has proposed the establishment of permanent tolerances for the combined residues of spinosad in/on the following stored grains: corn, oats, sorghum/milo, and wheat. The ARIA Team has concluded that available data support the establishment of permanent tolerances for the use of spinosad in/on the cereal grains crop group. Further, the additional uses

are not likely to pose an unacceptable risk to the U.S. population, infants or children, or any other subgroup of concern. The toxicology and residue chemistry databases are adequate to support the listed tolerances for the combined residues of spinosad and Section 3 registration for the use of spinosad in/on the cereal grains crop group excluding sweet corn. ARIA concludes that the proposed tolerances for spinosad in/on stored grains is adequate and appropriate and will not expose humans, animals or the environment to unreasonable adverse effects.

Cereal grains group (excluding corn, sweet)	1.5 ppm
Grain aspirated fractions	200 ppm
Rice hulls	4 ppm
Meat of cattle, goats, hogs, horse and sheep	1.5 ppm
Fat of cattle, goats, hogs, horse and sheep	33 ppm
Meat byproducts of cattle, goats, hogs, horse and sheep	8 ppm
Milk	6 ppm
Milk fat	75 ppm
Fat of poultry	0.5 ppm
Meat byproducts of poultry	0.03 ppm
Eggs	0.05 ppm

PHYSICOCHEMICAL PROPERTIES CHARACTERIZATION

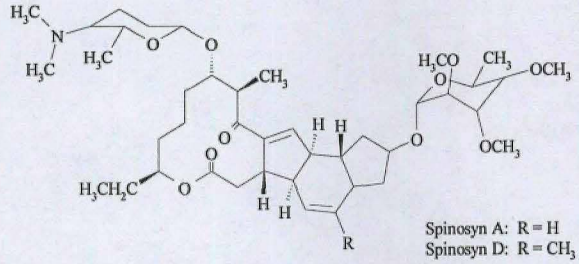
Identification of Active Ingredient

Spinosad [1]		
Common Name:	Spinosyn A	Spinosyn D
IUPAC Name:	(2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-2-(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1H-8-oxacyclododeca[b]as-indacene-7,15-dione	(2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bR)-2-(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1H-8-oxacyclododeca[b]as-indacene-7,15-dione
CAS Name:	(2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[(2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione	(2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)-2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-mannopyranosyl)oxy]-13-[[(2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione
CAS Number:	131929-60-7	131929-63-0
Company Name:	None	None
Other Synonyms:	Factor A	Factor D

[1] Spinosad is typically a mixture of Spinosyn A and Spinosyn D (85:15 ratio).

- Chemical Type: Insecticide
- PC Code Number: 110003
- Molecular Weight: 731 g/mol (Factor A), 745 g/mol (Factor D)

Structural Formula



Physical and Chemical Properties

Product chemistry data for spinosad were reviewed previously (Memo, M. Doherty, D276987, D272706 and D276890, 12-SEP-2001). There are no impurities present which are expected to cause residue concerns.

Selected physical and chemical properties of spinosad are summarized in Table 1.

Table 1. Physicochemical Properties of Spinosad Factors A and D

Property	Spinosyn A	Spinosyn D
Vapor Pressure, mm Hg	2.4×10^{-10}	1.6×10^{-10}
Melting Point, °C	84 - 100	161 - 170
Water Solubility, ppm		
pH 5	290	28.7
pH 7	235	0.332
pH 9	16	0.053

Spinosad is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

HAZARD ASSESSMENT

The existing toxicological database for spinosad supports the establishment of permanent tolerances for residues of spinosad and its metabolites in/on cereal grains crop group; aspirated grain fractions; rice hulls; meat, meat byproducts, and fat of cattle, goats, hogs, horse and sheep; milk; milk fat; meat byproducts and fat of poultry; and eggs.

Hazard Profile

Spinosad is classified as Toxicity Category III for acute oral, dermal toxicity and Toxicity Category IV for inhalation toxicity. It is classified as toxicity category IV for eye and skin irritation. It is not a dermal sensitizer. No dermal toxicity was seen at the limit dose in a 21-day dermal toxicity study in rabbits. For subchronic toxicity, the primary effects seen in the mouse were increased vacuolation of cells of the lymphoid organs, liver, kidney, stomach, female reproductive tract, and epididymis, and less severely in the heart, lung, pancreas, adrenal cortex, bone marrow, tongue, pituitary gland, and anemia. In rats, thyroid follicle epithelial cell vacuolation, anemia, multifocal hepatocellular granuloma, cardiomyopathy and spleenic histiocytosis were observed. In dog, microscopic changes in a variety of tissues, anemia, and possible liver damage were seen.

Spinosad is not a neurotoxic agent. No neurotoxic effects were seen at the limit dose in an acute neurotoxicity study in rats and at doses up to 42.7 mg/kg/day in a subchronic neurotoxicity study in rats. It is negative for mutagenicity in various mutagenicity assays. It is negative for carcinogenicity in rats and mice. In a chronic feeding study in dogs, toxicity such as increases in

serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid) were seen. Vacuolation of thyroid follicular cells, inflammation of thyroid, increased absolute and relative thyroid weights were observed in a chronic oral toxicity study in rats. In mice, rats and dogs, the liver, kidney, spleen, heart, thyroid, and bone marrow (anemia) appeared to be the target organs.

No developmental effects were seen in the rat and rabbit developmental toxicity studies. Decreased litter size and survival was observed in the presence of maternal toxicity (deaths) at the highest dose tested (HDT) in a 2-generation reproduction study in rats. Maternal and offspring toxicity (deaths) were equally severe, indicating no evidence of increased susceptibility in the 2-generation reproduction study in rats.

There were no major differences in the bioavailability, routes or rates of excretion or metabolism following a single low, high oral or repeated oral doses in rats. The feces were the major route of excretion. Approximately, 70-80% of the dose was absorbed with approximately 20% of the dose eliminated unabsorbed in the feces. The excreted metabolites were the glutathione conjugates of the parent and O-demethylated Factor A. Metabolites in the tissues were the N- and O-demethylated Factor A. Biliary excretion was rapid. Metabolites in the bile included the glutathione conjugates of the unchanged form, as well as N-and O-demethylated forms of Factor D.

Table 2. Acute Toxicity Profile of Spinosad

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral-Rat	43770701 43414515	LD_{50} = >2000 mg/kg	III
81-2	Acute Dermal-Rabbit	43414516	LD_{50} = >2000 mg/kg	III
81-3	Acute Inhalation-Rat	43414517	LC_{50} = >5.18 m/L	IV
81-4	Primary Eye Irritation	43414518	not an eye irritant	IV
81-5	Primary Skin Irritation	43414519	not a skin irritant	IV
81-6	Dermal Sensitization	43414520	not a skin sensitizer	n/a

Table 3. Toxicity Profile of Spinosad Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents-Mouse	43566602 (1992) Acceptable/guideline 0, 0.005, 0.015, 0.045 or 0.12% 0, 7.5, 22.5, 67.5, or 180 mg/kg/day	NOAEL = 7.5 mg/kg/day in males and females. Lowest observable adverse effect level (LOAEL) = 22.5 mg/kg/day in males and females; based on cytoplasmic vacuolation of lymphoid organs, liver, kidney, stomach, female reproductive tract, and epididymis. Other tissues less severely affected are heart, lung, pancreas, adrenal cortex, bone marrow, tongue, and pituitary gland.
870.3100 90-Day oral toxicity rodents-Rat	43566601 (1992) Acceptable/guideline 0, 0.05, 0.1, 0.2 or 0.4% 0/0, 33.9/38.8, 68.5/78.1, 133.5/151.6, or 273.1/308.2 mg/kg/day; M/F	NOAEL= 33.9 mg/kg/day in males; 38.8 mg/kg/day in females LOAEL= 68.5 mg/kg/day in males; 78.1 mg/kg/day in females based on adrenal cortical vacuolation in males, lymph node histiocytosis in both sexes.
870.3100 90-Day oral toxicity rodents-Rat	43557502 (1994) Acceptable/guideline 0, 0.003, 0.006, 0.012 or 0.06% 0/0, 2.2/2.6, 4.3/5.2, 8.6/10.4, or 42.7/52.1 mg/kg/day; M/F	NOAEL= 42.7 mg/kg/day in males; 52.1 mg/kg/day in females (HDT). LOAEL= Not observed in males and females.
870.3150 90-Day oral toxicity nonrodents-Dog	43444102 (1994) Acceptable/guideline 0, 150, 300, or 1350/900 (males) 900 (females) ppm 0/0, 4.89/5.38, 9.73/10.47 or 33.4/29.9 mg/kg/day; M/F	NOAEL= 4.89 mg/kg/day in males; 5.38 mg/kg/day in females LOAEL= 9.73 mg/kg/day in males; 10.47 mg/kg/day in females based on microscopic changes in a variety of tissues, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage.
870.3200 Repeated Dose Dermal Toxicity- Rabbit (21 days)	43557503 (1984) Acceptable/guideline 0, 100, 500 or 1000 mg/kg/day	NOAEL= 1000 mg/kg/day in males and females (HDT). LOAEL= Not observed.
870.3700a Prenatal developmental in rodents- Rat	43557505 (1993) 43770702 (1992; range finding) Acceptable/guideline 0, 10, 50 or 200 mg/kg/day	Maternal: NOAEL = 200 mg/kg/day (HDT). LOAEL = Not observed. Developmental: NOAEL = 200 mg/kg/day (HDT). LOAEL = Not observed.
870.3700b Prenatal developmental in nonrodents- Rabbit	43414521 (1994) 43770703 (1992; range finding) Acceptable/guideline 0, 2.5, 10.0 or 50.0 mg/kg/day	Maternal: NOAEL = 50 mg/kg/day (HDT). LOAEL = Not observed. Developmental: NOAEL = 50 mg/kg/day (HDT). LOAEL = Not observed.

Table 3. Toxicity Profile of Spinosad Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects- Rat	43701506 (1994) Acceptable/guideline 0, 0.005, 0.02 or 0.2% 0, 3, 10 or 100 mg/kg/day	Parental/Systemic NOAEL = 10 mg/kg/day . LOAEL = 100 mg/kg/day based on increases in heart, kidney, liver, spleen, and thyroid weights (both sexes), corroborative histopathology in the spleen and thyroid (both sexes), heart and kidney (males only), and histopathologic lesions in the lungs and mesenteric lymph nodes (both sexes), stomach (females only), and prostate. Reproductive NOAEL = 10 mg/kg/day. LOAEL = 100 mg/kg/day based on increased incidence of dystocia and/or vaginal bleeding after parturition with associated increases in mortality in the dams. Offspring NOAEL = 10 mg/kg/day. LOAEL = 100 mg/kg/day based on decreases in litter size, survival and body weights.
870.4100b Chronic toxicity- Dog	43701504 (1995) Acceptable/guideline 0, 50/60, 100/120 or 300/360 ppm 0/, 1.44/1.33, 2.68/2.72 or 8.46/8.22 mg/kg/day; M/F	NOAEL = 2.68 mg/kg/day in males, 2.72 mg/kg/day in females. LOAEL = 8.46 mg/kg/day in males; 8.22 mg/kg/day in females based on increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid).
870.4200 Carcinogenicity- Mouse	43701505 (1995) Acceptable/guideline 0, 0.0025, 0.008, or 0.036% 0, 25, 80, or 360 ppm 0/0, 3.4/4.2, 11.4/13.8, or 50.9/67.0 mg/kg/day; M/F	NOAEL = 11.4 mg/kg/day in males, 13.8 mg/kg/day in females. LOAEL = 50.9 mg/kg/day in males; 67.0 mg/kg/day in females based on decreased weight gains, increased mortality, the hematologic effects, and the gross finding of increased thickening of the gastric mucosa in females and the histologic changes in the stomach of males. No evidence of carcinogenicity.
870.4200 Carcinogenicity- Mouse	44123601 (1996) Acceptable/guideline 0, 0.0008 or 0.024% 0/0, 1.1/1.3 or 32.7/41.5 mg/kg/day; M/F	NOAEL not established. LOAEL = 1.1 mg/kg/day in males; 1.3 mg/kg/day in females. No evidence of carcinogenicity.

Table 3. Toxicity Profile of Spinosad Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Chronic/ Carcinogenicity- Rat	43701507, 43710503 (1995) 0, 0.005, 0.02, 0.05 or 0.1% 0/0, 2.4/3.0, 9.5/12.0, 24.1/30.3 or 49.4/62.8 mg/kg/day; M/F	NOAEL = 9.5 mg/kg/day in males, 12.0 mg/kg/day in females. LOAEL = 24.1 mg/kg/day in males; 30.3 mg/kg/day in females based on vacuolation of the epithelial follicular cells of the thyroid in both sexes. No evidence of carcinogenicity.
870.5265 Reverse Mutation Assay	43414522 (1992) Unacceptable/guideline	In the Ames Test (MRID 43414522), the mutation rates observed after treatment *of Salmonella typhimurium* strains (TA1535, TA1537, TA98, and TA100) and one strain of *Escherichia coli* (WP2/uvrA) with XDE105 increased in a dose-related manner when compared to the vehicle control. The colonies were shown in a replica plate assay to be predominately auxotrophs and not revertants. No growth of auxotrophs is expected in the Ames assay, but their presence an this assay suggests that XDE-105 supported their growth. The investigators noted that trace amounts of histidine and other amino acids were present in the test substance, which is a fermentation product. Therefore, an Ames assay with XDE-105 may not be appropriate, and this assay is considered to be unacceptable.
870.5300 Mouse lymphoma cell/mammalian activation gene forward mutation assay	43414523 (1992) Acceptable/guideline 0, 1, 5, 10, 15, 20 or 35 µg/ml 15 through 50 µg/ml with metabolic activation.	In a forward mutation assay using mouse lymphoma cells (MRID 43414523), Spinosad did not induce forward mutations in mouse lymphoma L5178Y Tk+/- cells at concentrations of 0, 1, 5, 10, 15, 20 or 35 µg/ml without metabolic activation or at concentrations of 15 through 50 µg/ml with metabolic activation.
870.5375 *In Vitro* mammalian cytogenetic assay	43414524 (1992) Acceptable/guideline 20, 26, or 35 µg/ml 100, 250 or 500 µg/ml with metabolic activation.	In a chromosomal aberrations assay, Spinosad did not increase the number of CHO cells with chromosome aberrations at concentrations of 20, 26, or 35 µg/ml without metabolic activation or at concentrations of 100, 250 or 500 µg/ml with metabolic activation.
870.5385 Micronucleus Assay	43414525 (1992) Acceptable/guideline 0, 500, 1000 or 2000 mg/kg/day	In a mouse micronucleus test, Spinosad did not increase the frequency of micronuclei in replicate assays with bone marrow cells from ICR mice treated with doses of 0, 500, 1000 or 2000 mg/kg/day for two consecutive days.

Table 3. Toxicity Profile of Spinosad Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5550 Unscheduled DNA Synthesis	43414526 (1992) Acceptable/guideline 0.01 to 5 µg/ml 10 to 1000 µg/ml	In the unscheduled DNA synthesis assay using primary rat hepatocytes, Spinosad did not induce unscheduled DNA synthesis (UDS) in adult rat hepatocytes *in vitro* at concentrations of 0.01 to 5 µg/ml. Concentrations from 10 to 1000 µg/ml of XDE-105 were cytotoxic.
870.6200 Acute Neurotoxicity -Rat	43557501 (1994) Acceptable/nonguideline 0, 200, 630 or 2000 mg/kg	NOAEL= 2000 mg/kg in males and females (HDT). LOAEL= Not established in both sexes.
870.6200b Repeat Dose Neurotoxicity-Rat	43557504 (1993) Acceptable/nonguideline 0, 0.003, 0.006, 0.012 or 0.06% 0/0, 2.2/2.6, 4.3/5.2, 8.6/10.4 or 42.7/52.1 mg/kg/day; M/F	NOAEL= 42.7 mg/kg/day in males; 52.1 mg/kg /day in females (HDT). LOAEL= Not established in both sexes.
870.6200b Repeat Dose Neurotoxicity-Rat	43701507, 43701503 (1995) Acceptable/guideline 0, or 0.1% 0/0 or 46.0/57.0 mg/kg/day, M/F	NOAEL= 46.0 mg/kg/day in males; 57.0 mg/kg/day in females (HDT). LOAEL= Not established in both sexes.

Table 3. Toxicity Profile of Spinosad Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics - Rat	43701508 (1995) Acceptable/guideline 10 or 100 mg/kg (single oral dose) 10 mg/kg (repeated dose 14 days)	At high (100 mg/kg) and single or multiple low (10 mg/kg) doses, there are no major differences in the bioavailability, routes or rates of excretion or metabolism of ^{14}C-XDE-105 (Factor A) following oral administration. The feces were the major route of excretion (82 to 87% of the doses at 168 hours after dosing), and ~7-10% of the dose was excreted in the urine. Approximately 70-80% of the dose was absorbed with ~20% of the dose eliminated unabsorbed in the feces. Blood levels of ^{14}C after the single and multiple 10 mg/kg doses were highest at 1 hour in both sexes. These levels were reduced by half 6 hours (males) and 12 hours (females) after dosing indicating that blood levels remain high for longer periods of time in female rats than in male rats. Blood levels of ^{14}C after the 100 mg/kg dose were highest at 6 and 2 hours in males and females, respectively. Concentrations of ^{14}C-XDE-105 at the time plasma concentrations were half the maximum value, suggested that the test material was still undergoing distribution. At 168 hr after administration of the low dose, the kidney, liver and fat of males and females had higher levels than other tissues. In the high dose group however, the adrenals (females only), kidney, lymph nodes, fat, and thyroids had higher levels than other tissues. The total radioactivity remaining in the tissues and carcass of the low and high dose animals was <0.6% and <3% of the administered dose, respectively. Also, at 7 days after the 100 mg/kg dose of XDE-105 (Factor A), the radioactivity observed in fat was 3-fold higher in female rats (40.978 µg equivalents/g tissue) than male rats (13.227 µg/g of tissue). The primary metabolites excreted were identified as the glutathione conjugates of the parent and O-demethylated XDE-105 (Factor A). Metabolites in the tissues were characterized as the – and O-demethylated (Factor A). The absorption, disposition, and elimination of ^{14}C-XDE-105 (Factor A) demonstrated no appreciable differences based on, dose or repeated dosing.

Table 3. Toxicity Profile of Spinosad Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics - Rat	43701509 (1995) Acceptable/guideline 100 mg/kg (single dose)	Results of these experiments indicated that at 100 mg/kg dose, the feces were the major route of excretion (84 to 92% of the dose at 168 hours after dosing), and 3-5% of the dose was excreted in the urine. Greater than 68% of the administered radioactivity was recovered in the feces within the first 24 hours following dosing. The excretion kinetics was biphasic with the α and ß excretion halftimes ($t_{½}$) of approximately 6 and 30 hours, respectively. The primary metabolites excreted were identified as the glutathione conjugates of the parent and O-demethylated XDE-105 (Factor D). Metabolites in the tissues were characterized as the – and O-demethylated (Factor D). The absorption, disposition, and elimination of ^{14}C-XDE-105 (Factor D) demonstrated no appreciable differences based on, dose or repeated dosing.
870.7485 Metabolism and pharmacokinetics - Rat	43701510 (1995) Acceptable/guideline 100 mg/kg (single dose, bile cannulated)	The feces contained from 23 to 55% of the dose (an average of 34%), and the bile had an average of approximately 36% (range of 28 to 40%) of the administered radioactivity. Approximately 21% of the dose was found in the tissues and carcass (range of 12 to 26%). The urine and CO_2 accounted for 3.3 and <0.1% of the dose. The bile excretion rate results suggested an uptake phase for the first 4 hr after dosing which preceded a biphasic decrease in the biliary excretion rate. The maximum rate of bile excretion was ~644 µg equivalents per hour at 2-4 hr; then the rate decreased to ~123 µg equivalents per hour at the 12-24 hr interval. The results of the study suggested that metabolites in the bile included the glutathione conjugates of the unchanged form, as well as – and O-demethylated forms of XDE-105 (Factor D).

FQPA Considerations

The FQPA SFC met on July 29, 2002 and recommended that a traditional additional safety factor of 10X can be removed for spinosad exposures and risks based on the following (Memo, B.Tarplee, HED document # 013341, 07-AUG-2002):

- The toxicological data base for spinosad is complete for FQPA assessment.

- No Special FQPA Safety Factor is necessary because: 1) there is no evidence of increased susceptibility of rat or rabbit fetuses following *in utero* exposure in the developmental studies with spinosad, and there is no evidence of increased susceptibility of young rats in the reproduction study with spinosad; 2) there are no residual uncertainties identified in the exposure databases; 3) EFED has indicated that the dietary drinking water exposure is based on conservative modeling estimates, and (4) HED Residential SOPs were used to assess post-application exposure to children as well as incidental oral exposure of toddlers, so these assessments do not underestimate the exposure and risks posed by spinosad.

A summary of the FQPA uncertainty factors (UF) chosen for spinosad and associated rationales are listed in Table 4.

Table 4. Summary of FQPA Safety Factors for Spinosad

	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	Incomplete Database (UF_{DB})	Special FQPA Safety Factor (Hazard and Exposure)
Magnitude of Factor	1X	1X	**1X**	1X
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	**Database is complete and developmental neurotoxicity study is not required**	No residual uncertainties regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases.
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**All dietary and non-dietary residential exposure assessments**	Not Applicable

Dose Response Assessment

Acute Dietary Endpoint: The HIARC did not select a dose and endpoint for an acute dietary risk assessment due to the lack of toxicological effects of concern attributable to a single exposure (dose) in studies available in the data base including oral developmental toxicity studies in rats and rabbits. In the acute neurotoxicity study, the NOAEL was 2000 mg/kg/day (HDT). **This risk assessment is not required.**

Chronic Dietary Endpoint: The chronic toxicity study in dogs was used to select the endpoint for establishing the chronic RfD of 0.027 mg/kg/day. The NOAEL of 2.68 mg/kg/day was based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels seen at the

LOAEL of 8.22 mg/kg/day. The hazard-based FQPA factor was reduced to 1X and a 100-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variation) was incorporated into the chronic RfD. The FQPA Safety Factor committee determined that a special FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.027 mg/kg/day.

Carcinogenicity: The HIARC classified spinosad as "not likely to be carcinogenic to humans" by all relevant routes of exposure based on adequate studies in two animal species; therefore, a cancer risk assessment is not required.

Short-Term Incidental Oral Endpoint: A short-term incidental oral endpoint was selected from the subchronic feeding study in dogs. The NOAEL of 4.89 mg/kg/day was based on microscopic changes in multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage seen at the LOAEL of 9.73 mg/kg/day. Toxicological effects seen in this study (anemia, clinical chemistry and histopathology) could occur in less than 90 days, although not evaluated at earlier time points in this study. Clinical signs of toxicity (minimal) were observed during treatment period of 1-4 weeks. Therefore, the study endpoint and duration is appropriate for this risk assessment.

Intermediate-Term Incidental Oral Endpoint: An intermediate-term incidental oral endpoint was selected from the chronic toxicity study in dogs. The NOAEL of 2.68 mg/kg/day was based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels seen at the LOAEL of 8.22 mg/kg/day. This study and endpoint are appropriate for the route and durations of exposure.

Dermal Penetration: No dermal absorption study is available. No dermal absorption factor was estimated because quantification of dermal and cancer risk is not required.

Short-, Intermediate-, and Long- Term Dermal Endpoint: The HIARC did not select a dose or endpoint for Short-,Intermediate-and Long-Term dermal risk assessments because: 1) lack of concern for pre and/or post natal toxicity; 2) the combination of molecular structure and size as well as the lack of dermal or systemic toxicity at 1000 mg/kg/day in a 21-day dermal toxicity study in rats which indicates poor dermal absorption; and 3) the lack of long-term exposure based on the current use pattern. No hazard was identified, therefore, quantification of dermal risk assessment is not required.

Short-term Inhalation Endpoint: A short-term inhalation endpoint was chosen from the subchronic feeding study in dogs. The NOAEL of 4.89 mg/kg/day was based on microscopic changes in a multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage seen at the LOAEL of 9.73 mg/kg/day. No inhalation toxicity study is available in the data base. Toxicological effects seen in this chosen oral study (anemia, clinical chemistry and histopathology) could occur in less than 90 days, although not evaluated at earlier time points in this study. Clinical signs of toxicity (minimal) were observed during treatment period of 1-4 weeks. Therefore, the

study endpoint and duration is appropriate for this risk assessment.

Intermediate-term and Long-Term Inhalation Endpoints: Intermediate- and long-term inhalation endpoints were chosen from the chronic toxicity study in dogs. The NOAEL of 2.68 mg/kg/day was based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels seen at the LOAEL of 8.22 mg/kg/day. The selected NOAEL is the lowest NOAEL for a chronic study which is suitable for exposure duration of concern.

MOE for Occupational/Residential Risk Assessments: A MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for the inhalation route of exposure. No dermal risk assessment for any exposure duration is required. A MOE of 100 is required for residential risk assessments for all routes of exposure for any duration. For short-/intermediate-/long-term inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) was converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs or LOAELs, since all of the inhalation endpoints are based on oral equivalents.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 5.

Table 5. Summary of Toxicological Endpoint Selection for Spinosad

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary females 13-50 years of age	This risk assessment is not required. No endpoint of concern attributable to a single exposure was identified.		
Acute Dietary general population including infants and children	This risk assessment is not required. No endpoint attributable to a single exposure of concern was identified for the general population, including infants and children.		
Chronic Dietary all populations	NOAEL= **2.7** UF = **100** **Chronic RfD** = **0.027** mg/kg/day	1x	**Chronic Toxicity Study in Dogs** LOAEL = **8.22** mg/kg/day based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels.
Incidental Oral Short-Term (1 - 30 Days) Residential Only	NOAEL= **4.9** mg/kg/day MOE= 100	1x	**Subchronic Feeding Study in Dogs** LOAEL = **9.73** mg/kg/day based on microscopic changes in multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage.

Table 5. Summary of Toxicological Endpoint Selection for Spinosad			
Exposure Scenario	**Dose (mg/kg/day) UF /MOE**	**Hazard Based Special FQPA Safety Factor**	**Endpoint for Risk Assessment**
Incidental Oral Intermediate-Term (1 - 6 Months) Residential Only	NOAEL= **2.7** mg/kg/day MOE = 100	1x	**Chronic Toxicity Study in Dogs** LOAEL = **8.22** mg/kg/day based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels.
Non-Dietary Risk Assessments			
Dermal (Any Time Period)	**N/A**	N/A	**Dermal risk assessment is not required.** Short-, Intermediate-, and Long-Term dermal risk assessments are not required because: 1) lack of concern for pre and/or post natal toxicity; 2) the combination of molecular structure and size as well as the lack of dermal or systemic toxicity at 1000 mg/kg/day in a 21-day dermal toxicity study in rats which indicates poor dermal absorption; and 3) the lack of long-term exposure based on the current use pattern.
Residential	N/A		
Occupational	N/A		
Inhalation Short-Term (1 - 30 days)	Oral NOAEL= **4.9** mg/kg/day		**Subchronic Feeding Study in Dogs** LOAEL = **9.73** mg/kg/day based on microscopic changes in a multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage.
Residential	MOE = 100	1x	
Occupational	MOE = 100	N/A	
Inhalation Intermediate-Term (1 - 6 Months)	Oral NOAEL= **2.7** mg/kg/day		**Chronic Toxicity Study in Dogs** LOAEL = **8.22** mg/kg/day based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels.
Residential	MOE = 100	1x	
Occupational	MOE = 100	N/A	
Inhalation Long-Term (>6 Months)	Oral NOAEL= **2.7** mg/kg/day		**Chronic Toxicity Study in Dogs** LOAEL = **8.22** mg/kg/day based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglyceride levels.
Residential	MOE = 100	1x	
Occupational	MOE = 100	N/A	
Cancer	**Classification: Not likely to be carcinogenic to humans.** **Q1*** = N/A Risk Assessment not required.		

Use 100% inhalation absorption factors for inhalation risk assessments when an oral NOAEL is selected.
N/A = not applicable.

Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, spinosad may be subjected to additional screening and/or testing tobetter characterize effects related to endocrine disruption.

EXPOSURE ASSESSMENT

Proposed Use

Dow AgroSciences has requested a Section 3 registration for spinosad use in/on cereal grains. Spinosad would be applied to prevent damage to stored grain from grain insect pests including the lesser grain borer, Indian meal moth, Angoumois grain moth, rice weevil, granary weevil, maize weevil, red-flour beetle, saw-toothed grain beetle, flat grain beetle. The rates of application vary from 0.64 dry oz. Entrust® (0.032 lb a.i.) per 1,000 bushels to 1.20 dry oz. Entrust® (0.06 lb a.i.) per 1,000 bushels depending upon grain species.

NAF - 313 rates of application vary from 4.0 fl oz (0.03125 lb a.i.) per 1,000 bushels to 7.8 fl oz (0.061 lb a.i.) per 1,000 bushels depending upon species of grain. One application is permitted. Spinosad will be applied as a coarse spray to the grain "stream" as it is augered or conveyed to a silo or similar storage facility. A summary of proposed uses is presented in Table 6.

Table 6. Proposed Uses and Use Sites

Crop Site	stored grain: barley, birdseed, corn, cotton seed, oats, peanuts (in shell), rice, sorghum/milo, soybeans, sunflower, wheat
Pest	lesser grain borer, Indian meal moth, Angoumois grain moth, rice weevil, granary weevil, maize weevil, red-flour beetle, saw-toothed grain beetle, flat grain beetle.

Formulation	Entrust® (EPA Reg. No. 62719 - 282) an 80 % wettable powder and NAF - 313 (EPA Reg. No. 62719 - 291) a 1.0 lb active ingredient per gallon liquid soluble concentrate.
Application Method	coarse spray to grain "stream" as augered or conveyed
Application Rate	0.031 - 0.061 lb a.i./1,000 bushels; @nominal rate of 1 ppm
Application Number	1 application
Restricted Entry Interval	4 hours
Manufacturer	Dow AgroSciences

Summary of Registered Uses

Spinosad is an insecticide of the Naturalyte class of compounds developed by Dow AgroSciences. It is highly active against target insect pests, but has low toxicity to mammals and most non-target insects. Spinosad is a broad spectrum insecticide, which acts by disrupting binding of acetylcholine in nicotinic acetylcholine receptors at the postsynaptic cell. Spinosad will be applied via wettable powder or liquid soluble concentrate as a coarse spray to grain "stream" as augered or conveyed. Permanent tolerances have been established under 40 CFR §180.495(a) for spinosad *per se*, in or on a wide variety of RACs at levels ranging from 0.02 to 10 ppm. Time-limited tolerances in conjunction with Emergency Exemption registrations have also been established for a wide variety of RACs at levels ranging from 0.02 - 15 ppm, and are listed under 40 CFR §180.495(b). Spinosad is also registered for use on residential turf.

Residue Profile

Permanent and temporary tolerances have been established for spinosad as listed in 40 CFR 180.495. Spinosad is registered for use on a number of agricultural commodities, including corn, sorghum, wheat oats, barley, buckwheat, rye, apples, Brassica vegetables, fruiting vegetables (excluding cucurbits), and tuberous and corm vegetables. The present analysis includes the published tolerance values together with a Section 3 proposed use on stored grains. The tolerance levels for stored grains were based on residue data submitted to support the porposed Section 3 action and are based on samples collected from locations. The submitted residue data for cereal grains report a maximum spinosad residue level of 1.4 ppm. A detailed residue chemistry review was conducted with this action (W. Cutchin, 10/13/04, D304201).

Nature of the Residue - Plants and Livestock

The qualitative nature of the residue in plants and livestock is adequately understood based on metabolism studies conducted with apples, cabbage, cotton, tomatoes, turnips, ruminants, and poultry (Memo; Issues Presented to the Metabolism Committee (MARC), G. Herndon, 03-FEB-1998). The HED MARC determined (Memo, G. Herndon, D243816, 03-MAR-1998) that only the parent compounds (spinosyns A and D) should be regulated in plant and animal commodities. Based on structure/activity relationships, the Committee determined that the

spinosad metabolites/fermentation impurities (spinosyns Factor B, Factor B of D, Factor K, and other related Factors) were of no more toxicological concern than the two parent compounds (spinosyns Factor A and Factor D). Therefore, spinosyns A and D are the residues of concern with respect to risk assessment.

Magnitude of the Residue - Stored Grains: Dow AgroSciences submitted magnitude of the residue studies conducted with wheat, corn, rice, barley, and oats. Stored grains were treated with a target application of 1 ppm (the nominal application rate) in six trials with wheat and corn and three each for rice, barley and oats. A total of 21 trials were conducted across seven locations, with sampling intervals of zero to three months or zero to eleven months. The treated grains were analyzed for residues of spinosad using adequately validated methods (storage intervals were also validated). Based on the available magnitude of the residue data, ARIA made the following conclusions.

Wheat - ARIA concludes that the wheat magnitude of residue data support a tolerance for residues of spinosad of 1.5 ppm on stored wheat grains. No additional magnitude of residue data are necessary.

Corn - ARIA concludes that the corn magnitude of residue data support a tolerance for residues of spinosad of 1.5 ppm on stored corn grains. No additional magnitude of residue data are necessary.

Rice - ARIA concludes that the rice magnitude of residue data support a tolerance for residues of spinosad on stored rice of 1.5 ppm. No additional magnitude of residue data are necessary.

Barley - ARIA concludes that the barley magnitude of residue data support a tolerance for residues of spinosad on stored barley grains of 1.5 ppm. No additional magnitude of residue data are necessary.

Oats - ARIA concludes that the oat magnitude of residue data support a tolerance for residues of spinosad on stored oat grains of 1.5 ppm. No additional magnitude of residue data are necessary.

HED concluded (personal communication, R. Loranger) that the submitted data on cereal grains supported a crop group tolerance on cereal grains, even though sorghum was not included in the trails. Therefore, a crop group tolerance of 1.5 ppm is supported on cereal grains, excluding sweet corn. The residue data also support tolerances of 200 ppm on aspirated grain fractions and 4 ppm on rice hulls. Tolerances are also recommended on meat of cattle, goats, hogs, horse and sheep (4 ppm); fat of cattle, goats, hogs, horse and sheep (33 ppm); meat byproducts of cattle, goats, hogs, horse and sheep (8 ppm); milk (6 ppm); milk fat (75 ppm); fat of poultry (0.5 ppm); meat byproducts of poultry (0.03 ppm); and eggs (0.05 ppm)(W. Cutchin, 10/13/04, D304201).

860.1500 Crop Field Trials

Field Trial Magnitude of the Residue In or On Wheat Grain Seed

Six supervised crop field trials were conducted in Mississippi, Indiana, Texas, Kansas and California with wheat grain. Each of the six field trial sites consisted of single untreated control sample and three replicated treated samples. The treated samples received one application of spinosad at a rate of approximately 1 mg/kg grain with an application volume of 5 gallons of spray solution /1000 bushels of grain. Samples were collected at three sites with sampling intervals of 0, 3, 6, and 11 months and at three sites with sampling intervals of 0 and 3 months. Residues in the stored wheat ranged from 0.373 to 1.238 ppm at zero time after application and 0.649 ppm to 0.754 ppm at eleven months after application.. The analytical method was adequate for the quantitation of spinosad in/on stored wheat grains.

Field Trial Magnitude of the Residue In or On Corn Grain Seed

Six supervised crop field trials were conducted in Mississippi, Indiana, Kansas, Texas, and California with corn grain. Each of the six field trial sites consisted of single untreated control sample and three replicated treated samples. The treated samples received one application of spinosad at a rate of approximately 1 mg/kg grain with an application volume of 5 gallons of spray solution /1000 bushels of grain. Samples were collected at three sites with sampling intervals of 0, 3, 6, and 11 months and at three sites with sampling intervals of 0 and 3 months. Residues in the stored corn ranged from 0.397 to 0.767 ppm at zero time after application and 0.432 ppm to 0.632 ppm at eleven months after application.. The analytical method was adequate for the quantitation of spinosad in/on stored corn grains.

Field Trial Magnitude of the Residue In or On Rice Grain Seed

Three supervised crop field trials were conducted in Mississippi, Texas, and California with stored rice grain. Each of the three field trial sites consisted of single untreated control sample and three replicated treated samples. The treated samples received one application of spinosad at a rate of approximately 1 mg/kg grain with an application volume of 5 gallons of spray solution /1000 bushels of grain. Samples were collected at two sites with sampling intervals of 0, 3, 6, and 11 months and at one site with sampling intervals of 0 and 3 months. Residues in the stored rice ranged from 0.411 to 0.797 ppm at zero time after application and 0.449 ppm to 1.297 ppm at eleven months after application.. The analytical method was adequate for the quantitation of spinosad in/on stored rice grains.

Field Trial Magnitude of the Residue In or On Barley Grain Seed

Three supervised crop field trials were conducted in Indiana, Texas, and California with stored barley grain. Each of the three field trial sites consisted of single untreated control sample and three replicated treated samples. The treated samples received one application of spinosad at a rate of approximately 1 mg/kg grain with an application volume of 5 gallons of spray solution /1000 bushels of grain. Samples were collected at three sites with sampling intervals of 0 and 3 months. Residues in the stored barley ranged from 0.499 to 1.075 ppm at zero time after application and 0.430 ppm to 1.248 ppm at three months after application.. The analytical method was adequate for the quantitation of spinosad in/on stored barley grains.

Field Trial Magnitude of the Residue In or On Oat Grain Seed

Three supervised crop field trials were conducted in Indiana, Texas, and California with stored oat grain. Each of the three field trial sites consisted of single untreated control sample and three replicated treated samples. The treated samples received one application of spinosad at a rate of approximately 1 mg/kg grain with an application volume of 5 gallons of spray solution /1000 bushels of grain. Samples were collected at three sites with sampling intervals of 0 and 3 months. Residues in the stored oats ranged from 0.398 to 0.877 ppm at zero time after application and 0.270 ppm to 0.834 ppm at three months after application.. The analytical method was adequate for the quantitation of spinosad in/on stored oat grains, processed commodities (e.g., flour, corn oil, hulls, etc.), and meat, milk, poultry and eggs.

International Harmonization of Tolerances: Canada, Codex, and Mexico do not have maximum residue limits (MRLs) for residues of spinosad in/on the proposed crops. Therefore, harmonization is not an issue.

DIETARY EXPOSURE AND RISK

The spinosad chronic dietary exposure assessments were conducted using DEEM-FCID™ (Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96 and 1998 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (*i.e.*, apple pie) are linked to EPA-defined food commodities (*i.e.*, apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (*i.e.*, orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

Acute Food Exposure

Since no acute dietary endpoint was selected by HIARC, no acute dietary analysis was conducted.

Chronic Food Exposure

A chronic dietary exposure assessment (using tolerance-level residues, DEEM default processing factors, and assuming 100% CT for all proposed commodities) was conducted for the general U.S. population and various population subgroups in order to determine the exposure and risk estimates which result from the addition of cereal grains to the commodity residue list for spinosad. This analysis is based on a previous chronic dietary exposure assessment conducted

by HED in December, 2003 (T. Bloem, D296814, 12/16/03). However, the chronic dietary risk assessment conducted for this action is partially refined. Tolerances were used for most crop commodities. However, anticipated residues were used in the calculation of residues in edible animal tissues (meat and milk), and for the residue level in cereal grains and milled fractions. Tolerance level residues were used for poultry and eggs. Processing factors from processing studies were used for cereal grains. Finally, percent crop treated data for several crop commodities were based on data submitted to HED by the Biological Economic Analysis Division (BEAD). For cereal grains, the assessment assumed that 10% of the crop would be treated, based upon a maximum percent seed supply treated with chlorpyrifos-methyl of 8% for wheat and 5% for barley and oats (Report on FQPA Tolerance Reassessment Progress and Risk Management Decision for Chlorpyrifos methyl (Document # EPA-R-01-003; 1/01)); Spinosad is expected to replace chlorpyrifos-methyl. The estimated chronic dietary exposures for the U.S. population and all population subgroups, as represented by percent of the chronic Population Adjusted Dose (cPAD), is below HED's level of concern (< 100% cPAD). The estimated exposure for the U.S. population is 21% of the cPAD. The estimated exposure for the most highly exposed subpopulation, children 1-2 years, is < 52% of the cPAD. See Table 7 for a summary of the spinosad and chronic dietary exposure and risk estimates.

Table 7. Results of Chronic Dietary Exposure Analysis for Spinosad, compared against a cPAD of 0.027 mg/kg/day		
Population Subgroup	**Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	0.005160	19.1
All Infants (< 1 year old)	0.005603	20.8
Children 1-2 years old	0.013824	51.2
Children 3-5 years old	0.010957	40.6
Children 6-12 years old	0.007290	27.0
Youth 13-19 years old	0.004605	17.1
Adults 20-49 years old	0.004268	15.8
Adults 50+ years old	0.003921	14.5
Females 13-49 years old	0.004185	15.5

Drinking Water Exposure

At the present time, there are no surface or ground water monitoring data available for spinosad. The HED MARC determined that the residue of concern in water is spinosad *per se* (Memo, G. Herndon, D243816, 03-MAR-1998). The following is a summary of information provided by EFED (Memo, Larry Liu, 03-AUG-2002). There are no ground or surface water monitoring data available for spinosad (See D. Vogel et. al., 8/15/02, D284803 for a more detailed discussion of drinking water exposure to spinosad).

Environmental Fate Assessment

Spinosad (containing Factors A and D) and its degradates are not very persistent and are relatively immobile. The potential for its residues to leach to groundwater and runoff to surface water is very low. Spinosad (containing Factors A and D) is expected to dissipate rapidly in the environment with a low potential to leach or runoff to surface water. Slow metabolic degradation was observed only in flooded sediment (half-lives 161–250 days in the laboratory, >25 days outdoors). Transformation products (Factor B and N-demethyl spinosad Factor D) are persistent (half-lives >6 months) in aerobic soil metabolism studies, but are relatively immobile.

Spinosad Factors A and D degrade in aerobic laboratory soil with half-lives of 13 and 14 days, respectively. They photodegrade readily in sterile water (<1 day at pH 7) and on soil (about 10 days). Based on McCall's relative mobility comparison, Factor A has a low to slight mobility in sandy soils and is immobile in silt loam and clay loam soils. Although no mobility data have been provided for Factor D, it is 180X less soluble than Factor A and therefore Factor D is less

likely to leach in the soil or runoff to surface water. Spinosad is not volatile; vapor pressures (25°C) are 2.0 to 3.0 x 10^{-11} kPa. CO_2 is the only volatile degradate. In terrestrial field dissipation studies on bareground plots, the estimated half-life of Factor A, formulated as an emulsifiable concentrate, was 0.3-0.5 days, and residues accounted for 3.1% of the applied in the runoff but did not leach. When spinosad was applied directly to the water surface in outdoor aquatic microcosm dissipation studies, total spinosad residues in the water had an observed half-life of <1 day.

Spinosad Factors A and D are stable to hydrolysis in pH 5, 7, and 9 buffer solutions. In flooded sediment, spinosad moves readily from the water to the solid phases. Spinosad degrades slowly in anaerobic sediment with half-lives of 161-250 days. Degradation rates in aerobic sediment were not determined. In an aquatic microcosm study, spinosad residues in the sediment peaked at 8 days and had an observed half-life of >25 days.

The major transformation product of Factor A is Factor B (N-demethylated Factor A). The major transformation product of Factor D is N-demethylated Factor D (the Factor D analogue of Factor B). IUPAC names were not provided for either transformation product. In aerobic soil metabolism laboratory studies using the parent, both transformation products accumulated to >50% of the applied by 28 days and had observed half-lives of >6 months. Spinosad Factor B is relatively immobile; no information is available on the mobility of N-demethylated Factor D. Neither transformation product was identified in terrestrial field dissipation studies.

Ground and Surface Water EECs

There are no ground or surface water monitoring data available for spinosad. Tier I models, FIRST and SCI-GROW, were used to derive the surface water and ground water EECs, respectively. Application to turf provided the high exposure scenario; therefore, the drinking water EECs were derived from the use on turf.

Ground Water: SCI-GROW provides a groundwater screening exposure value for use in determining the potential risk to human health from drinking groundwater contaminated with pesticides. The ground water modeling generated a ground water EEC of 0.037 ppb for spinosad.

Surface Water: The predicted index reservoir concentrations for total residues using FIRST for the proposed use of spinosad generated acute and chronic surface water EECs of 25 and 2.3 ppb, respectively.

AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Chronic Aggregate Risk (Food + Drinking Water)

The chronic aggregate-risk assessment takes into account average exposure estimates from dietary consumption of spinosad (food and drinking water). The chronic-dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (< 20% of the cPAD) and all population subgroups (Table 7). The most highly exposed population subgroup was children 1-2 years old at < 52% of the cPAD. The Tier 1 EDWCs generated by

EFED are less than HED's calculated chronic DWLOCs for chronic exposure to spinosad in drinking water. Therefore, the chronic aggregate risk associated with the proposed uses of spinosad do not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 8 summarizes the chronic aggregate exposure estimates for spinosad residues.

Table 8. Chronic Aggregate Risk Summary

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Groundwater EDWC (µg/L)	Surface Water EDWC (µg/L)	Chronic DWLOC[2] (µg/L)
U.S. Population	0.027	0.005160	0.021840	0.037	2.3	760
All infants (< 1 year old)		0.005603	0.021397			210
Children (1-2 years old)		0.013824	0.013176			130
Children (3-5 years old)		0.010957	0.016043			160
Children (6-12 years old)		0.007290	0.019710			200
Youth (13-19 years old)		0.004605	0.022395			670
Adults (20-49 years old)		0.004268	0.022732			800
Adults (50+ years old)		0.003921	0.023079			810
Females (13-49 years old)		0.004185	0.022815			680

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)
[2] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000 \text{ / g / mg})}{\text{water consumption (liter / day)}}$$

The surface and ground water EDWCs were used to compare against back-calculated DWLOCs for aggregate risk assessments. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM) was subtracted from the cPAD to obtain the acceptable chronic exposure to spinosad in drinking water.

For the chronic scenario, the DWLOCs are 760 ppb for the U.S. population, 680 ppb for females (13-49 years), and 130 ppb for children 1-2 years old. The average EWDCs of spinosad in surface and ground water (2.3 ppb and 0.037 ppb, respectively) are less than HED's DWLOCs for spinosad in drinking water as a contribution to chronic aggregate exposure (Table 8). Therefore, HED concludes with reasonable certainty that residues of spinosad in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

Because HED considers the aggregate risk resulting from multiple exposure pathways associated

with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of spinosad on drinking water as a part of the aggregate chronic risk assessment process.

OCCUPATIONAL EXPOSURE

Use Pattern Summary

Spinosad in either formulation would be applied to prevent damage to stored grain (noted above) from grain insect pests including the lesser grain borer, Indian meal moth, Angoumois grain moth, rice weevil, granary weevil, maize weevil, red-flour beetle, saw-toothed grain beetle, flat grain beetle. The rates of application vary from 0.64 dry oz. Entrust® (0.032 lb a.i.) per 1,000 bushels to 1.20 dry oz. Entrust® (0.06 lb a.i.) per 1,000 bushels depending upon grain species.

NAF - 313 rates of application vary from 4.0 fl oz (0.03125 lb a.i.) per 1,000 bushels to 7.8 fl oz (0.061 lb a.i.) per 1,000 bushels depending upon species of grain. One application is permitted. Spinosad will be applied as a coarse spray to the grain "stream" as it is augered or conveyed to a silo or similar storage facility. The proposed use pattern is summarized in Table 6.

Occupational Pesticide Handler

For the proposed use pattern, HED believes that the individual who prepares the spray mixture (i.e, mixer/loader) is essentially the only person exposed. There is no "applicator" *per se* and "applicator" exposure was not assessed. Once the spray mixture is prepared, the spray is applied to the grain stream from nozzles mounted above an auger or conveyer as the grain is lifted into a silo or other storage facility. Further, HED believes that the mixer/loader (i.e., the applicator) will be exposed over short-term (1 - 30 days) durations. Based on communications with experts in the field of stored grain protection, up to 250,000 bushels of grain may be lifted into a silo per day during the harvest season. HED uses that figure as the basis of its estimate of handler exposure.

Chemical specific data were not available with which to assess pesticide handler exposure. Therefore surrogate data from studies in the Pesticide Handler Exposure Database Version 1.1 (August 1998) PHED SURROGATE EXPOSURE GUIDE were used to estimate handler (mixer/loader) exposure.

It is HED policy to assess handler exposure and risk using "baseline" personal protective equipment (PPE) which is comprised of long sleeved shirt, long pants, and shoes plus socks and to assess "baseline" plus the use of protective gloves or other PPE as might be necessary or appropriate. The proposed labels direct pesticide handlers to wear a long sleeved shirt, long pants and shoes plus socks.

On 11 July 2002, the HED Hazard Identification Assessment Review Committee (HIARC) met to discuss the adequacy of the toxicological database relative to the compound spinosad. Relevant to the assessment herein, the HIARC did not identify dermal toxicological endpoints. The HIARC cited the "1) lack of appropriate endpoints; 2) the combination of molecular structure and size as well as the lack of dermal or systemic toxicity at 2,000 mg/kg (acute dermal

toxicity study) and at 1,000 mg/kg/day in a 21-day dermal toxicity study in rats which indicates the lack of dermal absorption; and 3) the lack of long-term exposure based on the current use pattern."

However, the HIARC did identify a short-term (1 - 30 days) inhalation toxicological endpoint. The No Observable Adverse Effect Level (NOAEL) is 4.9 mg a.i./kg bw/day and the endpoints (effects seen) were microscopic changes in multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage. A Margin of Exposure (MOE) ≥ 100 is adequate to protect occupational pesticide handlers from exposures to spinosad. The HIARC classified spinosad as "not likely" to be a human carcinogen therefore a cancer risk assessment is not necessary. See the ATTACHMENT for a summary of the toxicological endpoints for use in risk assessment. See Table 9 for a summary of exposures and risks to pesticide handlers.

Table 9. Estimated Handler Exposure and Risk from the Use of Spinosad as a Stored Grain Protectant

Unit Exposure[1] mg a.i./lb handled	Applic. Rate[2]	Units Treated[3] Per Day	Average Daily Dose[4] mg a.i./kg bw/day	NOAEL[5] mg a.i./kg bw/day	MOE[6]
Mixer/Loader - Liquid - Open Pour					
Inhal 0.0012 HC	0.061 lb a.i./1,000 bushels	250,000 bushels/day	Inhal 0.000261	4.9	18,774
Mixer/Loader - Wettable Powder - Open Bag					
Inhal 0.0043 MC	0.061 lb a.i./1,000 bushels	250,000 bushels/day	Inhal 0.000937	4.9	5,229

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from Entrust® and NAF - 313 labels (62719 - 282 and 62719 - 291 respectively)
3. Units Treated are taken from communications with stored grain expert.
4. Average Daily Dose(ADD) = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg).
5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. Short-term inhalation NOAEL = 4.9 mg a.i./kg bw/day identified from a subchronic feeding study in the dog.

A MOE of 100 is adequate to protect occupational pesticide handlers. Since the calculated MOEs are > 100, the proposed use does not exceed HED's level of concern.

Post-Application Exposure

Typical post-application exposure is not expected since there are no crop advisors or agricultural workers. Treated grain is stored in silos or similar facilities and therefore not "entered" as one might for row crops or other agricultural uses. If stored grain were to be inspected, HED

believes any inhalation exposure would be negligible and would certainly be less than what has been estimated for the mixer/loaders as presented above. Therefore, the proposed use does not exceed HED's level of concern.

Reentry Interval (REI)

Spinosad is classified in acute dermal toxicity category III and toxicity category IV for acute inhalation, primary eye irritation and primary skin irritation. It is not a dermal sensitizer. Spinosad has a REI of four (4) hours.

CONCLUSION

ARIA concludes that occupational exposure and aggregate chronic risk estimates do not exceed the Agency's level of concern. The uses proposed in this Section 3 action should not pose an unacceptable aggregate risk to infants, children, or adults.

COMMODITY	TOLERANCE
Cereal grains group (excluding corn, sweet)	1.5 ppm
Grain aspirated fractions	200 ppm
Rice hulls	4 ppm
Meat of cattle, goats, hogs, horse and sheep	1.5 ppm
Fat of cattle, goats, hogs, horse and sheep	33 ppm
Meat byproducts of cattle, goats, hogs, horse and sheep	8 ppm
Milk	6 ppm
Milk fat	75 ppm
Fat of poultry	0.5 ppm
Meat byproducts of poultry	0.03 ppm
Eggs	0.05 ppm